DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
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FALLS CHURCH VA 22041-3258

REPLY TO
ATTENTION OF

MCMR-RCQ (70-1n)

14 August 2002

HSRRB Policy Memorandum 2002-06, Version 01

SUBJECT: Assent of Children and Parental Permission

1. REFERENCES.

a. 10 U.S. Code 980, *Limitations on Use of Humans as Experimental Subjects*

b. 32 Code of Federal Regulations (CFR) 219, *Protection of Human Subjects*

c. 45 CFR 46, Subpart D, *Additional Protections for Children Involved as Subjects in Research*, 14 November 2001

d. DOD Directive 3216.2, *Protection of Human Subjects and Adherence to Ethical Standards in DOD-Supported Research*, 25 March 2002

e. Army Regulation (AR) 70-25, *Use of Volunteers as Subjects of Research, 25 January 1990*

f. 66 Federal Register 20589 (April 24, 2001), *FDA Interim Rule, Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products*

g. Institutional Review Board Reference Book, PricewaterhouseCoopers LLP (2001)

2. HISTORY. This is the first version of The Army Surgeon General's Human Subjects Research Review Board (HSRRB) Policy Memorandum 2002-06. This version is effective 3 September 2002. Details of the history can be found in Appendix A.

3. PURPOSE. This policy is being written to provide guidance to the HSRRB and investigators about the requirements for obtaining the assent of children who are subjects of research and for obtaining parental permission.

4. SCOPE. This policy affects intramural and extramural research that is reviewed by the HSRRB and intends to use children as research subjects.

5. DEFINITION OF TERMS (45 CFR 46.402, or as otherwise cited).

a. "Children" are persons who have not attained the legal age for consent to treatments or procedures involved in the research, or are not otherwise emancipated, under the applicable law of the jurisdiction in which the research will be conducted.

b. "Assent" means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

c. "Permission" means the agreement of the parent(s) or guardian to the participation of their child or ward in research.

d. "Parent" means a child's biological or adoptive parent.

e. "Guardian" means an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care.

f. "Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (32 CFR 219.102(i)). The FDA offers as guidance the following examples of procedures that FDA believe to be of minimal risk to children: clean-catch urinalysis, obtaining stool samples, administering electroencephalograms, minimal changes in diet or daily routine, use of standard psychological tests, and tests of devices involving temperature readings orally or in the ear (66 Fed. Reg. 20589 (April 24, 2001), *FDA Interim Rule, Supplementary Information, IIC.*).

6. BACKGROUND. Children are not legally able to give their informed consent to participate as subjects of research. Therefore, to include a child in research, the principal investigator (PI) must obtain the permission of the parent(s) or guardian. However, the permission of a parent(s) or guardian is not always sufficient, absent the assent of the child. Children have varying levels of ability to understand proposed research, and will often express a willingness, or lack of willingness, to participate. To acknowledge the capacity of children to understand research, at least to some extent, and to demonstrate respect for a child's increasing autonomy, the PI must also obtain the assent of the child to participate in research in certain circumstances.

7. INITIAL CONSIDERATIONS.

a. According to 32 CFR 219.107(a), if an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, consideration shall be given to including individuals as IRB members who are knowledgeable about and

experienced in working with children. The HSRRB should evaluate whether their membership includes such individuals.

b. Before considering any child assent or parental permission requirements, the HSRRB must initially determine if the research is otherwise in compliance with 10 USC 980 and AR 70-25:

(1) 10 USC 980 prohibits using children as research subjects unless the research is intended to be beneficial to each child subject. The FDA has opined that there can be evidence of intent to benefit subjects in the placebo arm of placebo-controlled trials, and therefore it is possible for placebo-controlled research studies to be conducted with children. Such benefits to subjects in the placebo arm may include increased monitoring and care of subjects (66 Fed. Reg. 20589 (April 24, 2001), *FDA Interim Rule, Supplementary Information, IID.*).

(2) AR 70-25, 3.1o. requires that any risk involved be justified by the expected benefit to the child, and that the expected benefits are at least as favorable to the child as those presented by available alternatives (see also 45 CFR 46.405).

8. ASSENT AND PARENTAL PERMISSION POLICY. The assent and parental permission requirements come from AR 70-25 and 45 CFR 46, Subpart D, which is expressly made applicable to research supported or conducted by the DOD by DODD 3216.2, 4.4.1.

a. Research that is of No Greater Than Minimal Risk to Children. Adequate provisions must be made for soliciting the assent of children and the permission of their parents or guardians (45 CFR 46.404; AR 70-25, 3.1o.). 45 CFR 46.408 discusses these requirements:

(1) Assent of children is required when the HSRRB believes that children are capable of providing assent. The HSRRB will consider the child's age, maturity, and psychological state to determine if a child is capable of assenting (AR 70-25, 3.1o.; 45 CFR 46.408). This judgment may be made for all children as a class for a protocol, or for each child, as deemed appropriate (45 CFR 46.408). Seven years of age is considered a reasonable minimum age at which children may have the capability to be involved in some kind of assent process. Assent must be in writing (AR 70-25, 3.1o.), and the HSRRB will determine how assent must be documented (45 CFR 46.408(e)).

(2) The HSRRB may waive assent for some or all children if it determines that the capability of some or all of the children is so limited that they cannot be reasonably consulted, or a procedure involved in the research holds out a prospect for direct benefit that is important to the health or well-being of the child, and is available only in the context of research (AR 70-25, 3.1o.; 45 CFR 46.408). The decision to waive assent,

either categorically for all children or for a group of children or on a case-by-case basis, is to be made by the HSRRB, not by investigators or a child's parent(s). If assent is to be waived for a child, the child should not be given an assent form. However, the child should be given information about the research. If a child is given the opportunity to assent, the child's refusal to assent must be honored. Furthermore, even if it is determined that a child is capable of assenting, the HSRRB may still waive the assent requirement under circumstances in which consent may be waived in accordance with 45 CFR 46.116d. of Subpart A (i.e., research is no greater than minimal risk, a waiver will not adversely affect the rights and welfare of the subjects, research could not practicably be carried out without the waiver, and whenever appropriate, the subjects will be provided with additional pertinent information after participation). If assent has been waived for a child, the PI must still verbally inform the child about the research (e.g., the purpose of the research, why the child will be participating in the research, research-related procedures, etc.).

(3) Permission of each child's parent or guardian must be solicited in accordance with the consent requirement of 45 CFR 46.116 of Subpart A:

(a) Permission will be sought only under circumstances that provide the parent(s) or guardian sufficient opportunity to consider whether or not to approve of their child's participation, and minimize the possibility of coercion;

(b) Information will be in language understandable to the parent(s) or guardian;

(c) There will be no exculpatory language, through which the parent(s) or guardian is made to waive or appear to waive any legal rights, or release the investigator, sponsor, or institution from liability for negligence; and

(d) The basic elements of informed consent must be met (see 45 CFR 46.116(a) for these elements).

(4) Additional parental permission considerations from 45 CFR 46.408 include:

(a) Permission of one parent is sufficient (45 CFR 46.408(b)).

(b) If the HSRRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the parental consent requirements, provided an appropriate mechanism for protecting the children who will participate is substituted, and provided further that waiver is not inconsistent with federal, state, or local law (45 CFR 46.408(c)). Other child subjects for whom waiver of parental permission may be

appropriate include subjects of research dealing with HIV, pregnancy, alcohol or drug use, or mental health. State laws often govern whether and when a child can consent to medical treatment for such conditions. The law of the state where the research is conducted can be used as guidance when determining whether parental permission may be waived for a child to participate in medical research, as differentiated from treatment, that deals with such conditions. Mechanisms to protect children when parental permission has been waived may include the availability of an individual, independent from the research team, to counsel the child, or third-party monitoring of the consent process with the child. The FDA has not adopted this provision permitting waiver of parental permission; therefore waiver of parental permission pursuant to 45 CFR 46.408(c) is not permissible for FDA-regulated research (66 Fed. Reg. 20589 (April 24, 2001), *FDA Interim Rule, Supplementary Information, IIH.*).

(c) Permission by parent(s) or guardians shall be documented in accordance with 45 CFR 46.117, Subpart A (see 45 CFR 46.408(d)).

b. Research that is of Greater Than Minimal Risk to Children. The HSRRB may approve such research if the risk is caused by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being (45 CFR 46.405). Adequate provisions must be made for soliciting the assent of the children and permission of parents or guardians (apply the same assent, waiver, and parental permission provisions as in no greater than minimal risk research, above).

c. Impermissible Categories of Research Using Children. 45 CFR 46, Subpart D provides for approval of two more categories of research using children. However, neither category can be approved by the HSRRB because of the restrictions of 10 USC 980, as discussed in this policy. The two other impermissible categories are:

(1) research involving greater than minimal risk (including research that represents a minor increase over minimal risk) and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition (45 CFR 46.406).

(2) research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407).

9. THE ASSENT DOCUMENT AND PROCESS.

a. The assent document should be tailored for the child with respect to his/her level of understanding, and should use age-appropriate language. Information given should include what the study is about, a statement that participation is voluntary, why a child

qualifies, the procedures to be done, alternatives to the research, risks and benefits, anticipated discomforts, a discussion of confidentiality, and an assurance that a child may withdraw. There should be a signature block for the child, the person obtaining assent, and a witness, if a witness is required by the HSRRB. This policy does not prescribe a specific format for the assent document. Sample formats are attached as Appendices. For a younger child, an assent document should address the following questions (*IRB Reference Book*, Chapter 10):

(1) What is the name of the study?

(2) Why me?

(3) What is it for?

(4) What will I have to do? How long will it take?

(5) Will it hurt?

(6) Will I have to go away from home?

(7) Will my parents be there? Did they say it was okay?

(8) How will this help other children?

(9) Will I get better at the end?

(10) What if I want to stop? Will I get in trouble?

(11) Can I pick another study? Are there any other choices?

b. The parent(s) or guardian should be present during the assent process. There should be an opportunity for the child and the parent(s) or guardian to ask questions. Whenever possible, decision-making should be shared by the parent(s) or guardian and the child. The PI and the parent(s) or guardian should not put undue pressure on the child. A copy of the assent document must be provided to the child and the child's

parent(s) or guardian. Except as described above in this policy, a child's dissent should be honored.

Julie K. Zadinsky

Encl

JULIE K. ZADINSKY
COL, AN
Acting Chair, Human Subjects
Research Review Board

RECOMMEND APPROVAL/~~DISAPPROVAL~~

_____ DATE: 27 AUG 02
LESTER MARTINEZ-LOPEZ
Major General, MC
Chair, Human Subjects
Research Review Board

APPROVED/~~DISAPPROVED~~

FOR THE SURGEON GENERAL:

Kenneth L. Farmer Jr. DATE: 28 Aug 02
KENNETH L. FARMER, JR.
Major General
Deputy Surgeon General

APPENDIX A

HSRRB Policy Memorandum History

Version Number: 01

Version Date:

Effective Date:

Reason for Revisions: This is the initial policy.

Detailed List of Changes: N/A

APPENDIX B

Sample Assent Form to Participate in a Research Study
(For Children Ages 7 Through 11 Years)

Agreement to Participate in a Research Project
Assent Form, Ages 7 through 11 Years

TITLE OF PROJECT:	List the Title exactly as it appears on the Protocol and Consent Form
PRINCIPAL INVESTIGATOR:	Name, Title and Department

We are asking you to be in this research project. You do not have to agree to be in the project. Here are some questions and answers about the research project:

1. What is the project about? [Describe the project].

[Sample: We will try a new medicine called ribavirin to see if it works better than the medicine you are taking now. You will still take the medicine you are taking now.]

2. Why are we asking you? [Explain why the child is being asked to participate].

3. What will happen to you if you are in the research project? [Explain the procedures - How long will each procedure and the whole project take? What will the subject have to do? What will be done to the subject? Will the procedure hurt? Will it be uncomfortable? Will the subject have to be away from home? Will the subject's parents be there?].

4. Will I get hurt if I am in the project? [Explain any risks or discomforts that weren't discussed above].

[Sample: The new medicine might not work. It may make you feel worse. You could get a fever or an upset stomach. Your doctor and parents will look out for any problems. Be sure to tell your parents if you feel bad or if you think anything is wrong.]

5. Will the project help me? [Explain the benefits of participation].

[Sample: The children who are part of the study will help us find out if the new medicine works. If the new medicine does work, you may feel better.]

6. Will it help other children if I am in the project? [Explain how subject's participation may help other children, if applicable].

7. If I don't want to be in project, do I have other choices? [Explain alternatives to participation, including other available studies or courses of treatment].

[Discuss confidentiality of information and research data].

You should ask us any questions that you have.

ASSENT: If you agree to be in this research project, sign your name on this form. Even if you agree, you can quit at any time without getting in trouble or being punished. If you don't want to be in this research project, do not sign your name. A copy of this form will be given to you and your parent/guardian.

Printed Name of Participant: _____

Signature of Participant: _____

Date: _____

INDIVIDUAL OBTAINING ASSENT: I certify that I have explained to the above individual the nature and purpose of the study, potential benefits, and possible risks associated with participation in this study. I have answered any questions that have been raised.

Printed Name of Individual Obtaining Assent: _____

Title: _____ Date: _____

Signature: _____

WITNESS: I have witnessed the explanation of the research project to the participant. The participant was given an opportunity to ask questions, and the participant's questions, if any, were answered.

Printed Name of Witness: _____

Signature of Witness: _____

Date: _____

APPENDIX C

Sample Assent Form to Participate in a Research Study
(For Children Ages 12 Through 17 Years or Until Age of Majority)

Agreement to Participate in a Research Study
Assent Form, Ages 12 through 17 Years

TITLE OF PROJECT:	List the Title exactly as it appears on the Protocol and Consent Form
PRINCIPAL INVESTIGATOR:	Name, Title and Department

1. INTRODUCTION. [Sample: We invite you to participate in this research study. Before you decide whether or not to volunteer for this study, you must understand the purpose, how it may help you, what the risks are, and what is expected of you. Once you understand the study and if you agree to volunteer, you will be asked to sign this form. You will be given a copy of this form to keep. You can only be in the study if your parent(s) agree

This form gives you information about the study. The investigator will talk to you about the study and answer any question you have. We will ask you to sign this form to show that you understand the study. We will give you a copy of this form to keep. It is important that you know:

a. You do not have to join the study.

b. You may change your mind and drop out of the study at any time you want.

c. If we make any important change to the study, we will tell you about it and will ask you if you still want to be in the study.]

2. PURPOSE OF STUDY.

[a. Explain what the research study is about.

b. Explain why the child is being asked to participate and how/why he/she qualifies for the study.

c. Explain pre-existing medical conditions of the child, if applicable.

d. Include approximate number of participants.]

[Sample: We want to see if a drug called ribavirin helps in the treatment of children with hepatitis C. We now use a drug called interferon to treat hepatitis C. Interferon is approved by the Food and Drug Administration for use in children. Ribavirin is an experimental drug for children because it has not been tested on children. In tests on adults, using interferon and ribavirin together works better than using interferon alone.

We want to see if using interferon and ribavirin together works better for children too. We also want to find out what amount of ribavirin works best with interferon.]

3. PROCEDURE.

[a. Briefly explain the study design and treatment methods. Discuss clinical detail only as relevant to consent (i.e., to the risks, benefits, or burdens of the study).

b. Identify what is investigational about the study.

c. Specify the number of required inpatient or outpatient visits, other time commitments, number of venipunctures, amount of blood to be drawn (in household measures), test, exams, interviews, other burdens, etc. For example: How long will each procedure and the whole project take? What will the child have to do? What will be done to the child? Will the procedure hurt? Will it be uncomfortable? Will the subject have to be away from home? Will the subject's parents be there?

d. Explain how the treatment groups will be assigned, if applicable. If randomization will determine treatment assignment, explain it in simple lay terms. If the study is placebo controlled, subjects must be informed that there is a possibility that they will receive "no treatment" and the consequences of no treatment or withholding a previous treatment regimen should be discussed.]

[Sample: We will divide the children in the study randomly into three groups (like flipping a coin so you have an equal chance of being in any group). We will give all three groups a small amount of ribavirin. We will give one of the groups a larger amount of ribavirin. We will give the last group the largest amount of ribavirin. You should know that in adults, the largest amount of ribavirin worked the best and was safe, and that there is a two out of three chance that you will receive less than that amount. If you are in one of the two groups with lower amounts of ribavirin and you don't get better after 12 weeks, we will put you in the group to get the largest amount of ribavirin.

You will be taking two pills a day for one year. You will come to the hospital every month for an exam and tests to see if the medicine is working and to see if there are any bad side effects.

We will ask you to drop out of the study if:

- There are any bad side effects
- Your doctor thinks it is best for you
- The medicine is not working after 24 weeks]

4. POTENTIAL RISKS/DISCOMFORT.

[a. List all risks that are more than minimal (no greater probability or magnitude than those ordinarily encountered in daily life or during routine medical tests). Include physical, psychological, social, economic, legal, or other risks, where present. Explain any discomforts, pain, inconvenience, or burdens. Use simple language–for example, use "loss of hiar" instead of "alopecia" and "skin rash" instead of "dermatitis".

b. Describe the severity and probability of all material risks, and the implications, in understandable terms. Use a table for Common (21-100/100), Occasional (5-20/100), and Rare (<5/100) risks sorted by Immediate (1-2 days of treatment), Prompt (within 2-3 weeks before next course), Delayed (any later time during treatment), and Late (after completion of treatment) onset, if appropriate for the study.]

[Sample: There are some risks to the treatment you will be given in this study:

- Interferon shots can cause pain, redness, or swelling, and there may be some oozing form the spot where the needle went in.
- You may have an allergic reaction to either interferon or ribavirin.
- Sometimes, children who are given both drugs get headaches, fever, chills, and upset stomachs, like having the "flu". This usually gets better after a few shots.
- There are sometimes more serious side effects. Interferon can make you depressed (feel sad) and ribavirin can cause anemia (low iron). The two drugs together can cause coughing, itching, problems in breathing, dizziness, or thyroid problems.
- Rare mild side effects include diarrhea, stomach pain, dry skin, and eye infection.
- Rare serious side effects include weight loss, suicidal thoughts and attempts, and lung and liver problems that could lead to death.
- We will look for side effects when we examine you and take blood tests. Your doctor may have to lower the amount or stop giving the drugs if the side effects are serious.
- We do not know if the two drugs will help you or make you worse. There may be risks we don't know about. We will tell you if we find out about any new risks.]

5. BENEFITS. [Explain the expected benefits of participating in the study.]

6. ALTERNATIVES TO PARTICPATION. [Explain alternatives to participation, including other available research projects or courses of treatment. Clearly state what treatment will be offered or recommended and the risks/benefits involved if the volunteer declines to participate.]

[Sample: If your doctor thinks that any treatment other than what you will get in this study would be better for you, your doctor will tell you that and will not ask you to be in this study. The only treatment now used for hepatitis C is interferon, and it only works in 15-20% of children.]

7. CONFIDENTIALITY. [Discuss confidentiality of research information and data.]

[Sample: We will keep the records of this study confidential. We will not tell anyone you are in the study. Only the people working on the study will know your name. They will keep this information in case we have to find you later for medical reasons.]

8. ADDITIONAL ELEMENTS. [If applicable, include the following: Unforeseeable risks to embryo; termination of subject's participation by investigators; additional costs to subject to participate; consequences of withdrawing; how information about significant new findings will be provided to subjects.]

ASSENT. By signing this form, you agree that you have talked to your doctor about the study and understand it, and want to be in the study. You also agree that we have talked to you about the risks and benefits of the study, and about other choices. You may drop out of the study at any time and no one will mind and nothing will change about your medical care other than not being in the study. Please call the Principal Investigator, [Insert PI Name] at [Insert Number] if you have any questions. A copy of this form will be given to you and your parent/guardian.

Printed Name of Participant:_____

Signature of Participant:_____

Date: _____

INDIVIDUAL OBTAINING ASSENT: I certify that I have explained to the above individual the nature and purpose of the study, potential benefits, and possible risks associated with participation in this study. I have answered any questions that have been raised.

Printed Name of Individual Obtaining Assent: _____

Title: _____ Date: _____

Signature: _____

WITNESS: I have witnessed the explanation of the research study to the participant. The participant was given an opportunity to ask questions, and the participant's questions, if any, were answered.

Printed Name of Witness: _____

Signature of Witness: _____

Date: _____

APPENDIX D

HSRRB Assent Form Checklist

HSRRB Assent Form Checklist

HSRRB Log No. _____

Date Checklist Completed: _____ PI: _____

Date Checklist Updated: _____ Reviewer's Signature: _____

Elements	Is Element Addressed?			Comments
	Yes	No	N/A	
Elements of Informed Consent 32 CFR 219.116 that are appropriate for Assent Forms:				
A statement that the study involves research and an explanation of the purpose of the research.				
An explanation how/why the child qualifies for the study (i.e., pre-existing medical conditions, if applicable).				
A description of the procedures to be followed.				
A description of foreseeable risks, inconvenience and/or discomforts in simple language.				
A description of expected benefit(s).				
A statement that participation is voluntary.				
A statement that the child may discontinue participation and withdraw at any time without penalty.				
An invitation for the child to ask questions.				
A statement addressing the alternatives to participation.				
A statement describing the extent to which confidentiality of records identifying the child will be maintained.				
Language describing that permission will be obtained from the parents and that both parent and child will receive a copy of the form.				
A statement that a copy of the form will be given to the subject and their parent/guardian.				
A space for signature and date of the child (and witness where applicable).				
A space for signature and date of the individual obtaining assent.				
The document presented is legible, with adequate font size, at a reading level appropriate for the child's age.				

HSRRB Assent Form Checklist

HSRRB Log No. _____

Additional Comments